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Abstract

The variability of a set of biomedical signals, assumed to be functions of time associated to the same phenomenon, is analysed following some criterions. Firstly, when the signal source is unique, the variability may be, for one sensor in function of the time occurrence of the signals, for several sensors at the same time a spatial variability. The case of several sources corresponds to the inter subject variability, and the comparison of populations. Then the distinction between amplitude variability, time variability and shape variability is introduced. Functional Data Analysis is viewed as modelling the variability through time warping functions. These functions are either composed with the signals, leading to a lot of curve registration techniques well fitted to time variability cancellation, or composed with the normalised integral functions of the signals when they can be assumed to be positive. The later case is well suited to shape analysis and shape variability estimation around an averaged shape. The Integral Shape Averaging (ISA) and Corrected Integral Shape Averaging (CISA) algorithms are recalled. Two applications are then presented, including shape clustering. The first one is a very good correlation observed between the appearance of an obstructive sleep apnoea and a shape change of the P-waves of the ECG. The second one is related to the Ensemble Spontaneous Activity (ESA) recorded in the round window (near the cochlea). It is shown, by simulation, that the shape of the histogram of the ESA amplitude is very sensitive to a localised correlated firing of the fibres, possibly associated to Tinnitus, on the contrary of the classical objective index, i.e. the PSD amplitude at 1 kHz.

1. Introduction

The variability of signals involved in Biology or Medicine - the so called biomedical signals - is an evidence for everybody interested in these fields. But, at the question "what is variability?" the answer is often fuzzy or linked to the application. The most often, variability is the variability of a physical or physiological measure, represented by a standard deviation around a mean value, for further inclusion in statistical tests. A different aspect of variability concerns a domain of biomedicine which is supported by a lot of papers and communications since a lot of years, which is Heart Rate Variability. In this case the variability is not for one parameter, but it is represented by the departure from the trend of e.g. the RR curve in function of the beat number. In fact this variability is due, not only to the heart itself but also to the modulation by other rhythms like the circadian rhythms or respiration. Typically this later aspect of variability is more sophisticated than the precedent one. So, let us try to make some classification of the different aspects of variability. The first distinction could be on the number of sources, that is practically the number of subjects. Considering the case of one source, if there is only one sensor, the

variability will be analysed for one type of signal at different epochs. For example, it's the case of beat to beat variability of the ECG waves, or ERPs variability from trial to trial. If there are several sensors at a given time, we are dealing with spatial variability. In BSPM records, the involved study could be the QT dispersion [1] or the spatial shape dispersion of the ECG waves [2]. Of course the both can be combined for studying spatial variability from time to time. Considering the case of several sources, the main objective is the analysis of inter individual variability, allowing the clustering of populations. Another point of view, which is more directly connected to signal processing and analysis, is making a distinction on what is varying. Dealing, in this paper, with the whole signal and not with some parameter or feature extracted from it, we concentrate on what is known as amplitude variability, time variability and shape variability. These points are typically in the field of Functional Data Analysis (FDA), since the data are functions. Of course, the functions represented by sampled curves, appear as vectors, but the main advantage on classical Data Analysis is to make use of the composition of functions. In the following we'll explain, in Section 2, how FDA is suited to Time Variability and Shape Variability analysis and modelling. In Section 3 two applications are recalled to illustrate the advantage of averaging shapes for the discrimination of signals in function of subtle differences in their shapes.

2. Modelling signal variability with Functional Data Analysis

Functional Data Analysis is a field introduced by the statisticians' community in the last decade [3]. The main application in signal processing is the problem of curve registration, especially for biomedical signals, as an alternative to the classical ensemble synchronous averaging [4]. In the following, we analyze how this approach is involved in the modeling of time variability and shape variability.

2.1. Time variability

Assuming time variability in a set of signals or curves, implies that time t_i, when the amplitude y_i is observed, is in fact a random variable. Modelling time variability consists in looking for the best set of time warping functions allowing the best realignment (or registration) of the curves according to some criterion. The simplest case is when time variability is modelled by a random delay, or jitter. The realignment of the signals, using for example a fiducial point or the maximum of the cross correlation, leads to the classical ensemble or cross sectional averaging. Estimating the time warpings is a problem of time delay estimation. The second step in complexity is to allow random fluctuations both on the delay and on a time scale factor between the signals. Thus, the model can be written as follows:

$$x_i(t) = s(a_i t + d_i) + n_i(t) \quad (1)$$

In this model the observation $x_i(t)$ is a randomly scaled and delayed version of the template, or "shape function" s(t), added to a zero mean noise $n_i(t)$. This case, where all the signals (without noise) are the same shape, is analyzed in [5, 6]. The Integral Shape Averaging (ISA) provides a mean signal with the same shape, through a direct algorithm i.e. needing no optimisation process.When the time warpings may be non linear functions, an optimisation process takes into account all the signals in order to estimate both the warpings and the source signal generating all the observations through time transformations. The main and common hypothesis of the various techniques of curve registration (CR) is the monotony of the warping functions which are generally imposed to

be increasing. A lot of methods, depending on *a priori* information, have been produced. Among them the Dynamic Time Warping [7, 8] is probably the most popular one. But more recently, other methods like the Self Modelling Registration [9] which can be viewed as an extension of Landmark Registration [10], with hidden landmarks [11].

According to the CR hypothesis, we can suppose that N signals are generated from the shape function *s(t)* as follows:

$$x_i(t) = a_i s(v_i(t)) + \varepsilon_i(t), \tag{2}$$

where the non-random function *s(t)* is the shape function, v_i are monotone increasing functions that account for time variability, and a_i and ε_i are random quantities that account for amplitude variability. We can write assuming zero mean process for ε_i and $E\{a\}=1$:

$$E\{x(t)\} = E\{s(v(t))\} \tag{3}$$

which can be approximated, for large N, by :

$$\bar{x}(t) = \frac{1}{N}\sum_{i=1}^{N} s(v_i(t)) \tag{4}$$

where $\bar{x}(t)$ is the classical average and is different, in general, from *s(t)* [35]. Therefore, the objective of the CR operation is to realign or register the signals to *s(t)*. This signal realignment permits to estimate the time warping functions $\left(v_i^{-1} = w_i\right)$, not directly observable. Then, an estimated shape function $\hat{s}(t)$ can be obtained as follows [35]:

$$\hat{s}(t) = \frac{1}{N}\sum_{i=1}^{N} x_i(\hat{w}_i(t)) \tag{5}$$

where, $\hat{w}_i$ are the estimated warping functions. The signal $\hat{s}(t)$ is unique when the following condition is verified:

$$\frac{1}{N}\sum_{i=1}^{N} \hat{w}_i(t) = t \ . \tag{6}$$

The main idea of the SMR method is to model the warping functions as linear combinations of a small number of functions as in following

$$w_i(t) = t + \sum_{j=1}^{q} \alpha_{ij}\phi_j(t) \tag{7}$$

The component functions ϕ_j are estimated from the signals. They are order p linear combinations of cubic B-spline, and then we can write:

$$\phi_j(t) = \sum_{i=1}^{p} c_{ji}\beta_i(t) \tag{8}$$

The parameters of the signal generation model defined in (2) can be estimated by integrated least squares minimization as follows:

$$\min F = \min \sum_{i=1}^{N} \int_{0}^{T} \left\{ x_i(t) - a_i s\left(v_i(t)\right) \right\}^2 dt \tag{9}$$

and in another form:

$$\min F = \min \sum_{i=1}^{N} \int_{0}^{T} \left\{ x_i(w_i(t)) - a_i s(t) \right\}^2 w_i'(t) dt \tag{10}$$

The objective function F is minimized by an iterative algorithm, given the estimated warping functions as follows:

$$\hat{s}(t) = \frac{\sum_{i=1}^{N} \hat{a}_i \hat{w}_i'(t) \hat{x}_i(\hat{w}_i(t))}{\sum_{i=1}^{N} \hat{a}_i^2 \hat{w}_i'(t)} \tag{11}$$

The example of SMR method was given to illustrate the possibility of modelling the warping functions. But the warpings are generally composed with the signals themselves. These tools are useful when we are looking for a biological time, like in [9], and when the set of signal shapes is homogeneous allowing increasing warpings of a common shape function. The end objective is often to cancel the time variability. But this variability may be also a source of information. As an example, the shape modifications of the P-wave during an exercise test was used in connection with a model of the depolarization of the system composed by the two auricles [12]. An alternative, avoiding the hypothesis of shape homogeneity is to compose the warpings with the normalized integral functions of the signals. As shown in the following, this alternative is more suited to shape analysis, allowing the computation of the averaged shape of a set of signals, and the shape variability around this average.

2.2. Shape variability

Now we introduce a new hypothesis: the signals are assumed to be positive on their supports. If this property is not verified by the data we can often work on positive functions of the signals, like taking their square of adding an offset or working separately on the positive and the negative parts of the signals… without significantly changing the clustering of the signal shapes.

The signals being positive, they become probability density functions (pdf) when they are normalized by the area under the curve, and the normalized integral functions are distribution functions (DF). Thus, the Distribution Function Method (DFM) [13] gives a natural warping $\varphi(t)$ between signals $s(t)$ and $v(t)$ with normalized integrals $S(t)$ and $V(t)$ respectively:

$$S(t) = V(t') = V(\varphi(t)) \tag{12}$$

The signals s and v being positive, the integrals S and V are increasing: thus the warping function $\varphi(t)$ on the normalized integrals, or its inverse function, is an increasing function since:

$$\varphi(t) = (V^{-1} \circ S)(t) \tag{13}$$

We can notice, derivating (12), that the warping on the normalized integrals, is not equivalent to the classical warping on the signals:

$s(t) = v(\varphi(t))\ \varphi'(t)$ (14)

The only case where the derivative of $\varphi(t)$ is a constant is when we can write:

$\varphi(t) = a.t + b,\ \ a>0$ (15)

This correspondence with such an affine function will be taken as the definition of shape equality. So, the departure of $\varphi(t)$ from a straight line is in fact a similarity criterion. Shape clustering may be done with this criterion but not in an optimal way, especially if we want to use unsupervised algorithms like k-means, since it is not a mathematical distance and because we need a technique to compute averaged shapes. This last point has been first provided by Integral Shape Averaging [5, 6]. Given a set of N positive signals $s_i(t)$, i = 1 to N, the inverse function of the normalized integral of the integral shape average is :

$$\Gamma_{ISA}^{-1}(y) = \frac{1}{N}\sum_{i=1}^{N} S_i^{-1}(y), \quad 0 < y < 1 \tag{16}$$

We can write:

$$S_i = \Gamma_{ISA} \circ \varphi_i \tag{17}$$

When all the signals are the same shape, i.e. scaled and shifted versions of the same shape function, ISA is optimal, giving an average signal with the same shape (on the contrary of the classical ensemble averaging) and with a mean position and a mean scale. In this case, the average is invariant to affine transformations of the signals.

When the signals are not the same shape, ISA gives an average shape, but the last property is not true. If we need an optimal algorithm we can use the Corrected Integral Shape Averaging (CISA) which takes into account the invariance property, by modelling the warping functions. In (17) the φ_i functions become:

$$\varphi_i = v_i \circ A_i \qquad \text{where } A_i(t) = \alpha_i t + \beta_i \quad \alpha_i > 0 \tag{18}$$

With some constraints of identifiability and an optimisation algorithm CISA provides both a mathematical distance and an average shape signal which is a centre of gravity, allowing a rigorous application of the k-means algorithm [14].

2.3. Applications

To illustrate the ability of clustering signal shapes, according to physiological properties of biomedical signals, we'll recall two applications. The first one concerns the shape of the P-waves of the ECG signal recorded during sleep from patients with Obstructive Sleep Apnoeas [14]. Using CISA algorithm two classes of P-wave shapes were found (on 7 patients) , very well correlated with the presence or not of apnoea episode. In fact the change in shape appeared at the beginning of the apnoea.

The second example concerns the Ensemble Spontaneous Activity (ESA) recorded in Guinea pigs, near the round window (cochlea). The application is linked to the explanation of Tinnitus, which is, up to now an open problem. An hypothesis, found in the literature, is that the ESA could present a localized correlated firing. The problem is that, even if

physiological experiments were available, the classical index i.e. the amplitude of the Power Spectral Density at 1 kHz, is unable to detect such subtle changes. It is shown in [15] by a simulation study that the shape of the ESA amplitude histogram is very sensitive to this correlation and could be a good detector for the acceptance or rejection of the hypothesis.

3. Conclusion

In conclusion, the interest of Functional Data Analysis is obvious for signal processing and analysis. If time variability can be assumed to be noise, then curve registration offers a rich panel of techniques. The warping functions, composed with the signals, may also bring information. The main restriction is that the warpings must be increasing functions, restricting the application to homogeneous sets of shapes. When signal are positive, the use of the warpings on the normalized integral functions, leads to shape clustering and shape statistics, with shape averaging techniques associated to a shape distance.

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